Learning to live with a poison planet

After public anxieties, special research laboratories are being set up to study the effects on people of food additives, pesticides and industrial chemicals, Pearce Wright reports

The study of poisons is probably the oldest science in the world, traceable back even further than the beginnings of astronomy. Under its modern name, toxicology, the science is emerging as a key science of the next century.

That importance is recognized in plans to establish university-based super science laboratories, or interdisciplinary research centres (IRCs), for studies of vital stategic importance. They include a £10 million IRC in the mechanisms of human toxicity, to be formed from the Medical Research Council's toxicology unit with Leicester university's departments of medicine and biology.

The plan reflects the health and safety anxieties of the public about the growing use of drugs, food additives, pesticides and industrial chemicals.

Although the latest estimates show that more than 70,000 synthetic chemicals are commonly used throughout the world, and that 500 new ones are introduced each year, a reminder that nature's poisons can be more potent than anything man-made came last week when a ban was placed on shellfish taken from Britain's north-east waters that were polluted by toxic algae.

Yet the study of precisely how the natural or man-made poisons harm living cells is a relatively young field of research. The biological action of only a few of the toxins is well understood.

Describing the goal of long-term research in toxicology, Dr Tom Connors, director of the MRC Toxicology Unit at Carshalton, Surrey, says: "If a mechanism of toxicity for a particular substance is properly understood, the possibility exists of designing an antidote to a poison or an analogue of a potentially useful compound without its hazardous side-effects."

Inevitably, the subject also raises the controversial issue of animal testing. In the past mice were sacrificed in the cause of medical research so that men did not die. Advances in understanding how brain damage might be caused by agents that have come under recent suspicion as neurotoxins, or as carcinogens in occupational and environmental pollutants, are emerging from new techniques of analysis, pioneered at Carshalton, that avoid animal studies.

Dr Connors says: "The new IRC will move research directly into studies of the effects in people of exposure to the myriad of chemical, rather than extrapolating from results of animal experiments into the likely effects on humans."

The pitfalls confronting the toxicologist are illustrated by the unpredictable and bewildering behaviour of substances in the body, whether accidentally or deliberately swallowed, inhaled or absorbed through the skin.

Dr John Timbrell, senior lecturer in toxicology at the School of Pharmacy, London University, sums up the hazards of toxic substances, saying: "There are no safe drugs; only safe ways of using them."

For instance, a couple of tablets of paracetamol, the successor to the aspirin as the popular painkiller, will dispose quickly of everyday aches and pains. Yet a dose of 22 tablets will take longer to act, and dispose of you permanently after a week with fatal liver damage.

The explanation is based on the existence of two pathways, or biochemical processes, in our body by which it can dispose of paracetamol.

Once the mechanism of paracetamol poisoning was unravelled, biochemists designed an antidote based on a substance called N-acetylcysteine, to be given either orally or intravenously within 10 to 12 hours.

The way the lethal process is triggered in an overdose, creating a by-product that poisons the liver, is described by Dr Timbrell in an *Introduction to Toxicology*, a fascinating non-specialist guide to the mysteries of poisoning; particularly in explaining toxigenesis, which are reactions after exposure with substances already in the body that then yield a life-threatening by-product.

Some conundrums that face the toxicologist border on the bizarre. An antibiotic called rifampicin, as well as neutralizing bacteria, has been found to speed the absorption by the body of contraceptive steroids, and is now believed to have resulted in unwanted pregnancies.

That sort of "cocktail" effect is recognized as of increasing importance, particularly in research into the carcinogens, the cancer-causing agents that can be hazards of occupational, environmental, medicinal or dietary origin.

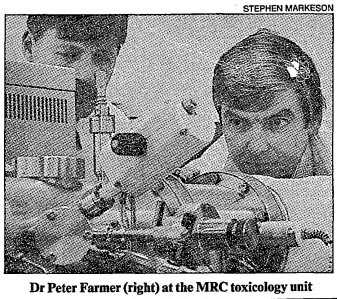
Since most cancer cases, responsible for up to 25 per cent of deaths in industrialized countries, derive from synthetic and natural chemicals, including tobacco smoke, toxicologists are trying to identify the most potent ones and their effects.

The research has a dual purpose, according to Dr Peter Farmer, of the MRC toxicology unit: development of more effective treatments for cancer and the long-term aim of prevention by eliminating exposure to harmful substances.

Poisons injure cells in different ways. Harmful substances such as lead salts, corrosives such as sulphuric acid, solvents such as carbon tetrachloride and the destructive weedkiller paraquat make a direct assault on cell architecture.

More potent ones block by more subtle intervention the body's normal production of essential enzymes, or behave like nerve poisons that prevent the release of the vital chemical messengers of the brain, or neurotransmitters. The botulism toxin, produced by the bacterium *clostridium botulinum*, is the most potent poison known. Less than one microgram is lethal. It binds irreversibly to the end of nerve fibres and blocks the release of the neurotransmitter acetylcholine.

A third type of injury is toxigenesis, and the sort of reactions that snake venoms precipitate by combining with other substance already present. Methanol poisoning is another. Antigenic reactions form a fourth class of poisoning, when substances harmless in themselves stimulate a lethal response by the body's defence system.



STEPHEN MARKESON

Dr Peter Farmer (right) at the MRC toxicology unit

The fifth category, and presently the cause of greatest concern, is carcinogenesis. Research into the processes implicated in turning healthy cells into cancerous ones is revealing a frightening number of elaborate and multi-step biochemical processes; some of which may be caused by exposure years before to a minute dose of a carcinogen.

A decisive step toward identifying the most hazardous molecules, and how they cause damage at levels which previously have been impossible to measure accurately, has been taken by Dr Farmer's group. The group's new method is known as molecular dosimetry, which measures the effects of exposure to small numbers of molecules of a suspect compound.

The procedure depends on a development called GC-MS, or gas chromotography-mass spectrometry, in which the scientists have refined and combined two of the most advanced techniques for fingerprinting complex substances in mixtures. The technique is based on a unique British instrument invented by VG Analytical.

Dr Farmer says: "We are all walking around with a lot of evidence in our body that tells the history of our exposure to carcinogens from work, the environment or our diets."

Much of the evidence is in the form of abnormal protein by-products left behind or sub-microscopic damage done to the cell's DNA, but which are characteristic of exposure to specific agents, he says.

With the new method of GC-MS analysis, his team conduct bio-assays of volunteers, using tests that have the unbelievable ability to detect a change caused by a carcinogen down to one modification in a cell. In effect, the monitoring programme by the MRC toxicologists is an audit of the "biochemical inventory" accumulated by individuals.

Apart from those tumours thought to be caused by viruses, it is believed most tumours are the result of exposure to one or more carcinogens.

Tests of the GC-MS method of pinpointing involves the screening of red blood cells from volunteers for signs of tell-tale damage from exposure to ethylene oxide, an environmental carcinogen in polluted air from cars, cigarette smoke and industrial processes.

Dr Farmer, in the course of this work, expects to make a conclusive comparison between the biological effects of active and passive smoking. Another project is looking at placenta cells for signs of benzpyrene damage, and others involve examination of occupational groups for factory exposures to a variety of medically suspect compounds.

The technique is not restricted to the toxicology of carcinogens. In addition, the MRC scientists have devised another method of screening for a type of brain damage that is caused by exposure again to very low levels of toxin and takes a long time to develop.

They have perfected a version of the scheme for detecting the condition called delayed neuropathy specifically for testing and screening the organophosphate type compounds that are used widely as pesticides.

The advance should play an important part in moves to get rid of the animal test devised in 1927, the LD50 test, that has tarnished the image of toxicology research and that many scientists find as offensive as the animal rights groups.

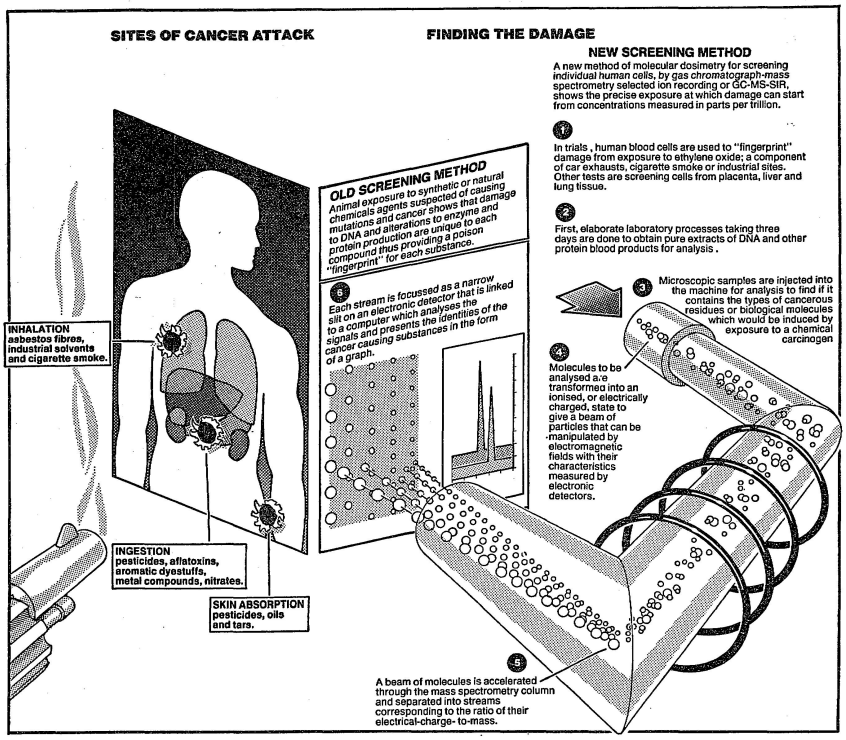
Yet the new screening technique comes from investigations into a disorder that has been something of the mystery for 60 years. The breakthrough comes from an understanding of how the nervous system is damaged by "organophosphate-induced delayed polyneuropathy syndrome", or OPIDP.

The disorder is comparable to a delayed version of the nerve gas poisoning from contamination with organophosphorus compounds, and better known for their acute action as chemical warfare agents and pesticides.

Two outbreaks of the syndrome affecting many thousands of people in 1930 and 1959 were traced to the misuse of organophosphorous mixtures used in lubricants, hydraulic fluids and as an ingredient in plastics. Exactly how the damage was done remained a mystery.

Apart from the reports of the two major disasters, much of the experience of the syndrome has come from successful treatment of attempts of suicide with insecticides and from accidental long-term occupational exposure.

● *Introduction to Toxicology by J.A. Timbrell is published by Taylor Francis at £19.95.*



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